Multiples of Minimal Alveolar Concentration of Volatile Agents Are Not Necessarily Equipotent

To the Editor:
I read with interest the article titled, “Isoflurane Causes Greater Neurodegeneration Than an Equivalent Exposure of Sevoflurane in the Developing Brain of Neonatal Mice,” in the June 2010 issue of Anesthesiology by Liang et al. The entire premise of the article is based on the assumption that 0.5 MAC of isoflurane is equipotent to 0.5 MAC of sevoflurane. Furthermore, the authors not only assume that these partial MAC values are equipotent for motion on surgical stimulation (the original comparative endpoint for MAC in humans), but that they are also equipotent for neurodegeneration in the developing mouse brain. I would submit that neither assumption is valid.

As early as 1970, Waud and Waud published an editorial in Anesthesiology explaining that MAC is only one point on an entire dose–response curve. This editorial inspired follow-up letters to the editor in support. I can find no evidence in the literature that, to date, the shape of the entire dose–response curve for percentages of patients showing motion on stimulation versus end-tidal concentration for any volatile agent has been established. For example, the percentage of patients who will move on surgical stimulation under 0.5 MAC versus 1.5 MAC, etc., remains unknown. There is certainly no assurance that the dose–response curve for any volatile agent will parallel any other dose–response curve for the volatile agents. Moreover, MAC is really a median minimal alveolar concentration, and there is no assurance that any specific MAC value holds true for any given patient or mouse.

In addition to the unverified assumption that partial MAC values are equipotent, even for percentages of patients moving with surgical stimulation, the authors go on to make the assumption that partial MAC values are also equipotent for an entirely different dose–response curve (neurodegeneration in the developing mouse brain vs. alveolar concentration). Even full MAC values for motion cannot be assumed to be equipotent between agents for a totally different dose–response curve. Likewise, if the equipotency of partial MAC values cannot be assumed for the original dose–response curve, it is at least equally invalid to assume equipotency of those partial MAC values when they are transferred to a totally different dose–response curve. The authors have not yet established a valid full MAC value for neurodegeneration in their study population. However, even if they did, there is no validity in assuming that partial MAC values for that dose–response curve would be equipotent, unless the authors determined the shape of the entire dose–response curve for each agent tested.

The authors only can assert with validity that, when given 0.5 MAC of isoflurane and 0.5 MAC of sevoflurane, there seems to be greater neurodegeneration in the developing mouse brain with isoflurane. The assertion that the mice have been administered equipotent doses of the two volatile agents can be supported by neither the definition of MAC nor the medical literature to date.

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References

In Reply:
We thank Dr. Cross for his insightful comments concerning our recent article. Dr. Cross makes several excellent points in regard to the nonlinear dose-response curves and the validity of partial minimum alveolar concentration (MAC) values.

In 1963, Merkel and Eger originated the term MAC, describing it as an “index of comparison” for different anesthetic agents. They defined 1 MAC as the end-tidal concentration of anesthetic that prevents movement in 50% of animals in response to a supramaximal stimulus. Subsequently, the use of MAC, to represent “a unifying concept of inhaled anesthetic potency” has grown to incorporate other clinical endpoints, such as MAC awake, MAC intubation, and MAC-BAR (blunt autonomic reflexes).

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The idea of partial MAC values has become part of the clinical jargon, and it is—more or less—an accurate reflection of partial potency because the slopes of the relationships for sevoflurane and isoflurane are quite similar. Moreover, it is common practice for patients as well as animals to use MAC multiples to compare the effects of various inhalational anesthetics on a wide variety of physiologic endpoints—for example, brain acetylcholine level, cerebral blood flow, vasoconstriction, cardiac function, and hemodynamics. In fact, many reviewers insist on the use of MAC multiples.

As Dr. Cross suggests, in terms of equal points on two separate dose-response curves for our study, a more precise comparison would have been 1 MAC isoflurane versus 1 MAC sevoflurane. Unfortunately, neonatal mice do not tolerate prolonged exposure to isoflurane at 1 MAC without developing confounding physiologic derangements. Thus, we used a lower concentration, that, by design, is commonly used clinically. This clinical applicability was an essential goal of our study, to compare the neurotoxicity of two agents at concentrations used clinically. We certainly agree with Dr. Cross that a more thorough method of comparing anesthetic neurotoxic potency would involve constructing full dose-response curves for apoptosis (or other endpoints) for each agent. Nevertheless, our results speak to common clinical practice as the immediate goal. We recognize that further work is necessary to establish the comparative mechanistic basis for these findings.

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References

8. Housmans PR, Murat I: Comparative effects of halothane, enflurane, and isoflurane at equipotent anesthetic concentrations on isolated ventricular myocardium of the ferret. II. Relaxation. Anesthesiology 1988; 69:464–71

Complications of C1-C2 Facet Injection

To the Editor:

The case report by Edlow et al. is a valuable example of the vascular nature of the C1-C2 facet injection. However, the most valuable picture that would have shown whether the complication that occurred was truly because of an unusual complication of the procedure or whether it was because of simple misplacement of the needle was not included. The anteroposterior view would show how lateral the needle was placed; instead, only the lateral view is provided. The picture of dye spread from the lateral view shows significant spread, much more than what would be expected if the injection occurred purely intraarticular. The classic needle location in an anteroposterior view should show the needle placed in the lateral two-thirds of the joint. Any other picture would explain why this complication occurred. Live fluoroscopy was not used and may have spared this patient from a complication.

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Reference


It Is Time to Abandon Atlanto-Axial Joint Injections: Do No Harm!

To the Editor:

We applaud Edlow et al. for publishing the case report of posterior circulation stroke after C1-C2 intraarticular facet steroid injection with evidence of diffuse microvascular injury. The same mechanism involved with cervical transforaminal epidural injections may be implicated in this case with vertebral artery penetration and embolic phenomenon, as the authors described. Complications at this level are not only related to vertebral artery penetration and similar to...